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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/033,526

11/02/2001

Yadong Huang

UCAL217

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01/24/2003

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EXAMINER

NICHOLS, CHRISTOPHER J

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 01/24/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application N .</b>	<b>Applicant(s)</b>	
	10/033,526	HUANG ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Christopher Nichols, Ph.D.	1647	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 24 December 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 7-22,25-27,29 and 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6,23,24,28 and 31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                     | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                            | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>5, 8</u> . | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

***Election/Restrictions***

1. Applicant's election with traverse of Group I (claims 1-6, 23-24, 28, and 31) in Paper No. 7 (21 November 2002) drawn to a method of inhibiting formation of neurofibrillary tangles in an individual said method comprising reducing formation of a carboxyl-truncated form of apoE is acknowledged. The traversal is on the ground(s) that it would not be unduly burdensome to perform a search of the inventions described in claims 1-31. This is not found persuasive because Groups I-VII represent 7 distinct and independent inventions. Each invention requires a separate and non-overlapping search. Furthermore, each invention has a separate and distinct classification. Therefore, examination of all 7 inventions as described in claims 1-31 would be a burdensome search. The restriction requirement between SEQ ID NO's 1-4 is hereby withdrawn. The restriction requirement between Groups I-VII is maintained. The election of species requirement for claim 4 is hereby withdrawn in view of the Applicant's argument and the prior art. It is noted, however, that claim 4 is read in view of claim 3 that requires apoE involvement in the pathology of the claimed disorders. This requirement is still deemed proper in regards to Groups I-VII and is therefore made FINAL.

***Status of Application, Amendments, and/or Claims***

2. Claims 7-22, 25-27, and 29-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 1-6, 23-24, 28, and 31 are under examination.

Art Unit: 1647

3. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

### *Specification*

4. The disclosure is objected to because of the following informalities: "four groups" should be "three groups" since only three forms are listed (pp. 61 paragraph [00233]).

Appropriate correction is required.

5. The use of the trademarks Aricept, Exelon, and Cognex has been noted in this application (pp. 33 paragraph [00140]). It should be capitalized wherever it appears and be accompanied by the generic terminology.
6. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. While claim 1 recites a goal (inhibiting formation...) it does not recite any method steps, such as administration of an agent.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/01101 (*15 January 1998 METHODS FOR THE TREATMENT OF APOLIPOPROTEIN E RELATED DISEASES*. Crutcher and Harmony). WO 98/01101 claims a method of treating conditions associated with apoE toxicity, including Alzheimer's disease and coronary artery disease, comprising administering a protease inhibitor, including antipain, to interfere with the production of neurotoxic fragments of apoE4 thus meeting the limitations of claim 1, 2, 3, 4, 5, 6 (Claims 1, 4, 14). While WO 98/01101 is silent with respect to neurofibrillary tangles in a neuronal cell in an individual with Alzheimer's disease, the specification discloses that reducing the amount of apoE4 tangles will have this effect. Thus the effect on Alzheimer's disease is inherent to the method of WO 98/01101. While WO 98/01101 is silent with respect to apoE4( $\Delta$ 272-299), it does not exclude apoE4( $\Delta$ 272-299) as a possible toxic fragment of apoE4 thus meeting the limitations of claim 6 (pp. 1 lines 8-16). WO 98/01101 also discloses a method of inhibiting the formation of neurotoxic apoE4 fragments in primary chick sympathetic neurons via protease inhibitors. WO 98/01101 teaches the use of antipain, a general serine protease inhibitor, to prevent the generation of toxic apoE4 fragments thus meeting the limitations of claim 28 (pp. 15 Example 5). Furthermore, WO 98/01101 claims a method of treating conditions associated with apoE toxicity, including Alzheimer's disease, comprising administering a

protease inhibitor, including antipain, to interfere with the production of neurotoxic fragments of apoE4 thus meeting the limitations of claim 28 (Claims 1, 4, 14). While WO 98/01101 is silent with respect to neurofibrillary tangles in a neuronal cell in an individual with Alzheimer's disease, the specification discloses that reducing the amount of apoE4 tangles will have this effect. Thus the effect on Alzheimer's disease is inherent to the method of WO 98/01101.

9. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5610297 (11 March 1997). US 5610297 discloses a novel class of peptide  $\alpha$ -ketoamides which selectively inhibit serine proteases. US 5610297 teaches the use of these serine proteases as neuroprotectants and therapeutics for the treatment of neurodegeneration and stroke thus meeting the limitations of claim 23 (Col. 1 lines 40-43). US 5610297 discloses a serine protease comprising the sequence "Ala-Ala-Pro-Leu" thus meeting the limitations of claim 24 (Col. 17 and 18). While US 5610297 is silent with respect to neurofibrillary tangles in a neuronal cell in an individual with Alzheimer's disease, the specification discloses that reducing the amount of apoE4 tangles will have this effect. Thus the effect on Alzheimer's disease is inherent to the method of US 5610297. Furthermore, the specification discloses that the enzyme which catalyzes the production of carboxyl-terminal fragments of apoE4 is susceptible to serine protease inhibitors.

10. Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Tolar et al. (19 August 1999 Truncated Apolipoprotein (ApoE) Causes Increased Intracellular Calcium and May Mediate ApoE Neurotoxicity. The Journal of Neuroscience **19(16)**: 7100-7110]. Tolar et al. discloses a method of using a protease inhibitor cocktail to attenuate the production of neurotoxic apoE4 fragments in dissociated chick, sympathetic neurons thus meeting the limitations of claim

31 (pp. 7102 “Protease inhibitors reduced the production of truncated apoE and attenuate Neurotoxicity of full-length apoE”; Figure 1). Tolar et al. uses a protein cocktail which includes antipain, a known serine protease inhibitor. While Tolar et al. is silent on reducing the activation of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE by A $\beta$ <sub>1-42</sub>, the specification demonstrates that said enzyme is susceptible to inhibition by serine protease inhibitors thus meeting the limitations of claim 31. Thus the effect on Alzheimer’s disease is inherent to the method of Tolar et al. Furthermore, Tolar et al. discloses that the protease inhibition reduces the formation of neurotoxic apoE fragments thus meeting the limitations of claim 31 (Figure 1, lower panel, western blot).

### *Summary*

11. It is of note that the Sigma Chemical Company catalog lists antipain as a non-selective serine protease inhibitor (Cat# A6191).
12. Claims 1-6, 23-24, 28, and 31 are hereby rejected.

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Art Unit: 1647

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*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher J. Nichols whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN  
January 17, 2003

*Elizabeth C. Kemmerer*

ELIZABETH KEMMERER  
PRIMARY EXAMINER